PHARMACEUTICAL COMPOSITION FOR ORAL USE COMPRISING AN ACTIVE PRINCIPLE LIABLE TO UNDERGO A LARGE FIRST INTESTINAL PASSAGE EFFECT

The invention relates to a novel composition for oral use comprising an active principle liable to undergo a large first intestinal passage effect. Statins and in particular simvastatin are more particularly illustrated as active principles.

It is known from the documents Drug Metab. Disp. (1995) 23: 279-84 and Transplantation (1992) 53: 596-602 that the intestinal metabolism plays an important role in the bioavailability of a certain number of active principles. Thus, studies have shown that the bioavavailability of an active principle can be improved by blocking or reducing the intestinal metabolism (see Clin. Pharmacol. Ther. (1997) 61: 401-9) rather than by acting on the metabolism of the liver. The solution consisting in blocking the intestinal metabolism has a certain risk since it acts directly on the regulatory system. Specifically, cellular transporters have a well-defined role whose regulation depends on the concentration of ligands in the lumen. If, for example, the ligand concentration decreases, the number of transporters increases.

The Applicant has thus sought to reduce the intestinal metabolism which a certain number of molecules undergo.

Although the invention concerns all active principles liable to undergo a first intestinal passage effect, this effect is described more particularly in relation to the statins and especially simvastatin, without, however, this being limiting.

The statins constitute a therapeutic family which acts by inhibiting hydroxymethylgutaryl (HMG) Coenzyme A-reductase, an enzyme which limits the synthesis of

cholesterol in the liver and stimulates the activity of the LDL (Low Density Lipoprotein) receptors. As a result of this mechanism of action, statins are essentially used as hypocholesterolemiant agents. A certain number of studies have moreover demonstrated that statins have a preventive effect on cardiovascular diseases, and also that they entail a regression of atheroma plaques. There are at present six statins, which are, respectively, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin and, finally, simvastatin, which is more particularly illustrated in the description hereinbelow.

Simvastatin is a prodrug obtained by synthesis from the fermentation product of *aspergillus terreus*. This molecule, which is well known, of empirical formula $C_{25}H_{38}O_5$, is a lactone whose activity is triggered by means of the enzymatic or chemical opening reaction of its lactone function. In practice, simvastatin is made active by hydroxylation to the β-hydroxy acid. Physically, simvastatin is in the form of a white crystalline powder which is virtually insoluble in water but highly soluble in chloroform, methanol and ethanol. After oral administration, simvastatin is hydrolysed after absorption in the intestine and the liver to its β-hydroxy acid form, its main metabolite, which is the source of the competitive and reversible inhibitory effect on HMG CoA-reductase.

Although simvastatin is indeed resorbed in the gastrointestinal tract (to a level of 90%), it nevertheless undergoes a strong first hepatic passage effect, in particular with cytochrome CYP 3A4. This phenomenon is described in particular in document Clin. Pharmacokinet 24(3): 195-202, 1993, which indicates that the systemic bioavailability of simvastatin is only 7% of the dose ingested. A solution for improving the bioavailability of simvastatin is to inhibit the action of cytochrome CYP 3A4 with inhibitors such as

itraconazole, detoconazole or grapefruit juice. However, this solution is unsatisfactory since it may lead, as already stated, to a deregulation of the metabolism. The Applicant has also found that simvastatin undergoes a strong first intestinal passage effect, a problem which, a priori, was not previously known for this molecule.

Consequently, the problem which the invention proposes to solve is that of improving the systemic bioavailability of active principles liable to undergo a strong first intestinal passage effect by minimizing this effect rather than by blocking it. Consequently, should the first hepatic passage effect exist, it will be greatly reduced since more molecules will be available in the liver.

To do this, the invention proposes the use of an oral pharmaceutical composition to reduce the intestinal passage effect on the active principle contained in, the said composition being in the form of a system which is self-microemulsifying on contact with an aqueous phase, comprising:

- a therapeutically effective amount of the said active principle;
- a lipophilic phase comprising a mixture of glycerol mono-, di- and triesters and of PEG mono- and diesters with at least one fatty acid chosen from the group comprising C_8-C_{18} fatty acids;
- a surfactant phase comprising a mixture of glycerol mono-, di- and triesters and of PEG mono- and diesters with caprylic acid (C_8) and capric acid (C_{10});
- a co-surfactant phase comprising at least one ester of a polyvalent alcohol with at least one fatty acid chosen from the group comprising caprylic esters of propylene glycol, lauric esters of propylene glycol and oleic esters of

polyglycerol,
- the ratio TA/CoTA being between 0.2 and 0.6.

The self-microemulsifying systems which are of concern in the invention are known under the name SMEDDS®, a trade mark registered by the Applicant meaning Self Micro Emulsifying Drug Delivery System, and are described more particularly in document EP-A-670 715 and the corresponding document US-A-6 054 136. The Applicant has found, equally surprisingly and unexpectedly, that the constituents of the SMEDDS® make it possible to increase the rate of dissolution of the active principles so that the enzymatic sites present on the intestinal villus and responsible for the first intestinal passage effect are rapidly saturated, this allowing to quickly make available the active principle in excess and then to increase the rate of absorption. Therefore, the SMEDDS® reduces the intestinal metabolism and thus increases the bioavailability of the active principle.

In the abovementioned documents, it is indicated that, as a result of the formation of the microemulsion on contact with an aqueous phase, SMEDDS® enable water-insoluble active principles to be dissolved, and consequently enable the bioavailability of the microemulsified active agent(s) they are transporting to be increased. More specifically, the SMEDDS® enables the insoluble active principle to be dissolved instantaneously by presenting it in the form of a multiparticulate supramolecular structure. The abovementioned documents therefore describe only the problem of solubility of the active principles, which is improved by the SMEDDS® formulation. It follows therefrom that the more the solubility increases, the more the bioavailability is improved.

However, no reference is made anywhere in these documents to the ability of SMEDDS® to increase the

rate of dissolution of the active principles, neither to the effect on the rate of absorption at the intestinal level which is improved. Thus, the Applicant has found, entirely surprisingly, that the incorporation of an active principle with a strong first intestinal passage effect into a self-microemulsifying system makes it possible to reduce the first intestinal passage effect, and thus to improve the systemic bioavailability of the active molecule. As already mentioned, the use of SMEDDS increases the rate of dissolution so that the intestinal enzymatic sites are rapidly saturated and the excess of the active principle is immediately made available in the blood circulation. As a consequence, the rate of absorption is increased, the availability of the active molecule in the liver is greater and the systemic passage is thus proportionally greater. The action does not therefore take place downstream (in the liver) but rather upstream (in the intestine).

The SMEDDS® may be, at ambient temperature, in solid or liquid form depending on the very nature of the fatty substances of which they are composed. Thus, if at least one fatty substance constituting the SMEDDS® has a melting point higher than ambient temperature, about 25°C, then the SMEDDS® will be solid at ambient temperature. On the contrary, if at least one fatty substance constituting the SMEDDS® has a melting point of less than about 25°C, then the SMEDDS® is liquid at ambient temperature. Consequently, the SMEDDS® may be incorporated into gel capsules in liquid form, optionally while hot, and then, depending on the nature of their constituents, remain liquid or become semi-solid at ambient temperature. The manufacturing process is relatively simple since it consists in mixing together all the constituents, including the active principle, with or without heating depending on the physicochemical characteristics of the fatty substances.

In the description hereinbelow and in the claims:

the expression "aqueous phase" denotes:

- either the in vivo physiological medium as it presents itself after ingesting the composition, and the pH of which varies as a function of the state of the gastrointestinal tract,
- or a reconstituted in vitro physiological medium, the microemulsion then being formed on simple contact with the aqueous phase, without ingestion,

- all the percentages are given in mg/g.

According to a first characteristic of the composition of the invention, the lipophilic phase comprises a mixture of glycerol mono-, di- and triesters and of PEG mono- and diesters with at least one fatty acid chosen from the group comprising saturated and unsaturated C_8-C_{18} fatty acids.

In practice, this mixture is obtained by an alcoholysis reaction of polyethylene glycol with a molecular weight of between 300 and 1 500 and of a hydrogenated plant oil itself consisting of a mixture in variable proportions, depending on its nature, of mono-, di- and triglycerides of at least one of the fatty acids described above. This same mixture may also be obtained by esterifying glycerol and PEG with a molecular weight of between 300 and 1 500 with at least one of the fatty acids described above, or alternatively by mixing esters of glycerol and ethylene oxide condensates with at least one of the said fatty acids.

In practice, the lipophilic phase has an HLB value of less than 20, preferably between 9 and 15, and represents between 1% and 99% by weight of the composition. In a first embodiment, the lipophilic phase predominantly comprises a mixture of glycerol

mono-, di- and triesters and of PEG mono- and diesters with the combination of saturated C_8-C_{18} fatty acids, has an HLB value equal to 14 and represents between 50% and 95% by weight of the composition. In practice, such a mixture is obtained by an alcoholysis reaction of PEG with a molecular weight of between 300 and 1 500 with an oil predominantly containing lauric triglycerides. A product corresponding to this definition is Gélucire® 44/14 sold by the Applicant. This product is fully defined in the 3rd edition of the European Pharmacopoeia under the definition lauric macrogolglycerides. In a second embodiment, the lipophilic phase comprises a mixture of glycerol mono-, di- and triesters and of PEG mono- and diesters with saturated and unsaturated C_{16}-C_{18} fatty acids. Products corresponding to this definition are the products Labrafil M1944CS and Labrafil M2125CS sold by the Applicant and in accordance with the monographs of the 3rd edition of the European Pharmacopoeia under the respective names "Oleoyl Macrogolglycerides" and "Linoleoyl Macrogolglycerides".

Moreover and as already stated, the surfactant phase comprises a mixture of glycerol mono-, di- and triesters and of PEG mono-, di- and triesters with caprylic acid and capric acid.

The surfactant phase may be obtained in the same manner as previously, by alcoholysis reaction starting with polyethylene glycol with a molecular weight of between 200 and 600 and a hydrogenated plant oil fraction which is rich in glycerol ester, with caprylic acid and capric acid. The surfactant phase may also be obtained by esterifying glycerol and polyethylene glycol with capric acid and caprylic acid, but also by mixing an ester of glycerol and ethylene oxide condensates with caprylic acid and capric acid. In practice, the surfactant phase has an HLB value of between 5 and 20.

A product corresponding to the definition of the surfactant phase is the product sold by the Applicant under the brand name Labrasol®, which corresponds to the monograph of the 3rd edition of the European Pharmacopoeia entitled "magrogol glycéride caprylocapric [caprylocapric magrogol glyceride]". In one advantageous embodiment, the surfactant phase represents between 1% and 30% by weight of the composition.

Moreover, and as already stated, the co-surfactant phase comprises at least one ester of an alcohol with at least one fatty acid.

The monoesters of propylene glycol chosen from the group comprising propylene glycol monocaprylate and propylene glycol monolaurate are more particularly preferred. The products sold by the Applicant and containing monoesters of propylene glycol and of caprylic acid are Capryol® 90 and Capryol® PGMC. Similarly, a product sold by the Applicant and containing propylene glycol monolaurate is Lauroglycol 90®.

In a first embodiment, the co-surfactant phase contains propylene glycol monocaprylate and represents between 3% and 32% by weight of the composition.

In a second embodiment, the co-surfactant phase contains propylene glycol monolaurate and represents between 1% and 8% by weight of the composition. In this case, Lauroglycol® 90 is advantageously used.

As already stated, the self-microemulsifying system as described above makes it possible to reduce the first intestinal passage effect of a certain number of active principles such as, for example, those belonging to the statin family, in particular simvastatin. Consequently, and in one particular embodiment, the statin is

simvastatin. Moreover, to be therapeutically effective, the simvastatin represents between 0.1% and 6% by weight of the composition and advantageously 4% by weight.

In a particular embodiment, the pharmaceutical composition comprises by weight (mg/g):

- between 0.1% and 6% of simvastatin,
- between 52% and 70% of Gélucire® 44/14,
- between 5% and 30% of Labrasol®,
- between 15% and 30% of propylene glycol monocaprylate.

In a first embodiment, the propylene glycol monocaprylate contained in this composition consists of Capryol® PGMC representing between 15% and 25% by weight of the composition. In a second embodiment, the monocaprylate consists of Capryol® 90 and represents between 20% and 30% by weight of the composition.

In one preferred form, the composition of the invention comprises:

- 4% of simvastatin,
- 65.2% of Gélucire® 44/14,
- 10.3% of Labrasol®,
- 20.5% of Capryol PGMC.

Alternatively, the composition comprises:

- 4% of simvastatin,
- 57.6% of Gélucire® 44/14,
- 12.8% of Labrasol®,
- 25.6% of Capryol® 90.

According to another embodiment, the pharmaceutical composition comprises by weight (in mg/g):

- 0.1% to 6% of simvastatin,

- between 52% and 70% of Gélucire® 44/14,
- between 6% and 30% of Labrasol®,
- between 1% and 8% of Lauroglycol® 90.

Advantageously, the composition of the invention contains:

- 4% of simvastatin,
- 65.3% of Gélucire® 44/14,
- 24.6% of Labrasol®,
- 6.1% of Lauroglycol® 90.

The invention also concerns a pharmaceutical composition for oral use that is in the form of a system which is self-microemulsifying on contact with an aqueous phase, comprising:

- a therapeutically effective amount of the said active principle;
- a lipophilic phase comprising a mixture of glycerol mono-, di- and triesters and of PEG mono- and diesters with at least one fatty acid chosen from the group comprising C_8-C_{18} fatty acids;
- a surfactant phase comprising a mixture of glycerol mono-, di- and triesters and of PEG mono- and diesters with caprylic acid (C_8) and capric acid (C_{10});
- a co-surfactant phase comprising at least one ester of a polyvalent alcohol with at least one fatty acid;
- the ratio TA/CoTA being between 0.2 and 6,

characterized in that the ester of a polyvalent alcohol with at least one fatty acid in the co-surfactant phase is chosen from the group comprising caprylic esters of propylene glycol.

Thus, the Applicant has found that the use of caprylic esters in the co-surfactant phase of the SMEDDS® compositions, not disclosed in the document EP-A-677

115, allowed to get a larger micro-emulsion area, i. e to get a microemulsion even in the presence of high proportions of water, when compared with the use of for example lauric esters of propylene glycol. Then, the SMEDDS® system allows, in the presence of caprylic esters of propylene glycol in the co-surfactant phase, to improve the dissolution of the hydrophobic active principles and to get stable compositions in the presence of high proportions of water, in accordance with the volume of the physiological liquid contained in the organism.

The lipophilic phase, the surfactant phase and the co-surfactant phase are defined and are used in the same proportions as previously disclosed, the use of the esters of propylene glycol being however limited to caprylic esters of propylene glycol, such as those commercialised by the Applicant under the name Capryol® PGMC and Capryol® 90.

In an advantageous embodiment, the ratio TA/CoTA is equal to 0,5.

The invention and the advantages arising therefrom will emerge more clearly from the following preparation example in support of the attached figures.

Figure 1 represents the average concentration of simvastatin in the plasma as a function of time.

Figure 2 represents the average concentration of hydroxysimvastatin in the plasma as a function of time.

Figure 3 represents a ternary diagram of a SMEDDS® composition comprising a laurate of propylene glycol as CoTA.

Figures 4, 5 and 6 represent ternary diagrams of a SMEDDS® composition comprising a caprylate of propylene

glycol or an oleic ester of polyglycerol, as CoTA.

Example 1

The following three formulations are manufactured:

COMPONENTS	*FORMULA 1*	*FORMULA 2*	*FORMULA 3*
SIMVASTATIN	4.0%	4.0%	4.0%
LABRASOL	10.3%	12.8%	24.6%
GÉLUCIRE® 44/14	65.2%	57.6%	65.3%
CAPRYOL® PGMC	20.5%	-	-
CAPRYOL® 90	-	25.6%	-
LAUROGLYCOL® 90	-	-	6.1%
TOTAL	100%	100%	100%

Each of the constituents of the formulae are mixed together at ambient temperature with stirring at between 60 and 100 rpm.

Example 2: Reduction in the intestinal barrier effect with the product which is the subject of the invention, relative to simvastatin alone, using human intestinal microsomes

The test is carried out in vitro using human intestinal microsomes containing:

- 20 mg/ml of proteins,
- 0.09 nmol/mg of cytochromes P450,
- 0.77 nmol/min/mg of cytochromes P450 3 A 4.

1 mg/ml of microsomes is then placed in contact:

- with a regenerating system having the following composition:
  - NADPH : 1 mmol
  - Glucose 6-phosphate dehydrogenase : 2 units/ml
  - Glucose 6-phosphate : 10 mmol

Potassium phosphate, pH 7.4	: 100 mmol
Magnesium chloride	: 10 mmol

followed by equilibration at 37°C for 3 minutes.

The reaction is then initiated by adding 12 µmol of simvastatin or of the composition of the invention to the reaction mixture. 100 µl aliquots are mixed with a solution of 400 µl of a 50/50 mixture of ice and acetonitrile at 0, 15, 30, 60, 120 and 180 minutes. Testosterone is tested in parallel as control component.

The level of simvastatin remaining is then quantified by HPLC and mass spectrometry.

The conditions for carrying out the HPLC are as follows:

- column	: Hypersil BDS C18, 30×2 mm i.d., 3 µm,
- buffer	: 25 mmol of ammonium hydroxide adjusted to a pH of 3.5 with formic acid,
- mobile phase	: A - 10% of buffer and 90% of water, B - 10% of buffer and 90% of acetonitrile,
- gradient	: 0% of B to 100% of B over 3 minutes, re-equilibration for 2 minutes,
- flow rate	: 300 µl/min
- injection volume	: 10 µl

The mass spectrometer used is known under the reference PE SCIEX 150.

The results are given in the following table. After 15 minutes, the testosterone has completely disappeared

from the cell medium. On the other hand, for the three compositions of the invention, between 20% and 23% of simvastatin remains in the circulation despite the first intestinal passage effect.

Test product \ Time in min	PERCENTAGE REMAINING					
	0	**15**	**30**	**60**	**120**	**180**
TESTOSTERONE	100	-	-	-	-	0
SIMVASTATIN	100	0	0	0	0	0
FORMULA 1	100	20.4	2.66	0.13	0.07	0.22
FORMULA 2	100	21.1	2.00	0.12	0.03	0.08
FORMULA 3	100	22.6	2.29	0.14	0.06	0.13

It can be deduced that the SMEDDS® allows to increase the rate of dissolution of simvastatin, then to more rapidly saturate the enzymatic sites and as a consequence to make the excess of simvastatin directly available by increasing the rate of absorption.

Example 3: Comparison of the relative bioavailabilities in vivo between formulae 1, 2 and 3 and a reference formula, namely Zocor®

To evaluate the influence of various concentrations of the composition of the invention on the relative oral bioavailability of simvastatin, four male Beagle dogs were treated in a crossed model (over 4 periods, one formulation per period and per dog, an interval of one week between each period) with the three formulations 1, 2 and 3 and a reference formulation, ZOCOR® sold by the Laboratoires Merck, Sharp & Dohme-Chibret.

The formulations were administered in the form of capsules, each comprising 40 mg of simvastatin. Each dog received two capsules, thus corresponding to a total dose of 80 mg. The dose administered of 80 mg per dog is assumed to give concentration profiles of simvastatin in the plasma that are comparable to those

observed in humans at high therapeutic doses (80 mg).

A blood sample was taken from each dog before the treatment and at successive times of 15 minutes, 30 minutes, 1 hour, 1½ hours, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours and 24 hours. The concentrations of simvastatin and of hydroxysimvastatin in the plasma were determined by HPLC/MS analytical method.

The results given in Figures 1 and 2, which represent the average concentrations of simvastatin (Figure 1) and of hydroxysimvastatin (Figure 2) in the plasma as a function of time for the three formulations and the reference formula (ZOCOR®).

After administration of the ZOCOR®, a delay in the absorption of simvastatin is observed. Specifically, simvastatin and hydroxysimvastatin are found in the plasma in all the animals only at and above the third sample, that is to say one hour after administration. In contrast, levels of simvastatin and of hydroxysimvastatin in the plasma are detected from the 15th minute after administration of formulae 1, 2 and 3. In other words, the composition of the invention increases the level of absorption.

The table below gives the average kinetic parameters (Cmax and Tmax) and absorption parameters (Vmax, T50% and T90%) for the reference formula ZOCOR® and formulae 1 to 3. In this table, the parameters have the following meanings:

Cmax : maximum level in the plasma (ng/ml)
Tmax : time to obtain Cmax (h)
Vmax : maximum level of absorption (% dose/h)
T50% : time to absorb 50% of the dose
T90% : time to absorb 90% of the dose

Parameters	**Reference**	**Formula 1**	**Formula 2**	**Formula 3**

Cmax	63.945	215.2125	249.49	203.84
Tmax	1	1.5	1	0.5
Vmax (%h)	19.71	57.84	62.14	62.91
T50% (h)	3	1.5	1.5	1
T90% (h)	22	5	3.5	3.5

As shown in the above table, the level of absorption is three times as high for the formulae of the invention compared with ZOCOR®. Consequently, a maximum concentration in the plasma for the formulae of the invention which is considerably higher than that of Zocor® is found.

The most significant difference between formulations 1, 2 and 3 and Zocor® concerns the improvement in the absorption. Specifically, after administration of formulation 1, the average area under the curve (AUC for simvastatin and for hydroxysimvastatin) is two to three times greater than the corresponding values for Zocor®.

The table below gives the levels of absorption as a function of time of simvastatin.

	Average level of absorption (V) *(% of the dose/h)*			
T(h)	**Ref.**	**1**	**2**	**3**
0	0.00	0.00	0.00	0.00
0.25	0.67	57.84	23.98	62.91
0.5	1.72	18.06	10.65	26.67
1	19.71	47.56	57.13	53.14
1.5	12.52	48.33	62.14	26.36
2	13.29	40.55	45.08	33.09
3	8.38	18.66	16.94	11.32
4	2.03	3.01	2.82	2.56
6	2.21	3.61	2.93	2.29
8	1.33	2.27	1.60	1.28
12	1.38	0.85	0.52	

24	1.01			

As shown in this table, the rate of absorption of simvastatin is close to 100 times greater for formulae 1 and 3 than for the reference formula. Formulation 3, for its part, shows that the nature of the constituents may be varied and thus the level of absorption may be varied directly. These results therefore demonstrate that an effect is being produced on the rate of dissolution of the active agent.

Moreover, the relative bioequivalence index resulting from the sum of the areas under the curve (AUC for simvastatin and hydroxysimvastatin for formulation 1 versus Zocor®) is 3.26. The relative bioequivalence corresponding to formula 2 is 2.88, and formula 3 is 2.66.

Consequently, even though a small decrease in the relative bioavailability between formulae 1, 2 and 3 is observed, the different concentrations of the components constituting these formulae do not induce a variation in the relative bioavailability of simvastatin in dogs.

Example 4

This example aims to demonstrate the ability of the SMEDDS® to form a micro-emulsion area, i. e to get a microemulsion in the presence of high proportions of water, when a caprylic ester of propylene glycol is used in the co-surfactant phase (in comparison with the lauric esters of propylene glycol used in formulae 1, 2 and 3 or with the oleic esters of polyglycerol).

The three following formulae were tested:

FORMULA	1	2	3	4
TA	LABRASOL	LABRASOL	LABRASOL	LABRASOL
Lipophilic phase	GELUCIRE 44/14	GELUCIRE 44/14	GELUCIRE 44/14	GELUCIRE 44/14
CoTA	LAUROGLYCOL 90	CAPRYOL 90	CAPRYOL PGMC	PLUROL OLEIQUE
Ratio TA/CoTA	0,5	0,5	0,5	0,5

Figures 3, 4, 5 and 6 represent the ternary diagrams of formulae 1 to 4.

The hatched area correspond to the area of micro-emulsion. This figures illustrate the fact that the micro-emulsion area is broader when a caprylic ester of propylene glycol is used instead of a lauric ester of propylene glycol or an oleic ester of polyglycerol.